What is the best approach to the evaluation of hirsutism?

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EVIDENCE-BASED ANSWER

The evaluation of hirsutism should begin with a history and physical examination to identify signs and symptoms suggestive of diseases such as polycystic ovarian syndrome (PCOS), hypothyroidism, hyperprolactinemia, hyperandrogenic insulin-resistant acanthosis nigricans (HAIR-AN) syndrome, androgenic tumors, Cushing's syndrome, or congenital adrenal hyperplasia (CAH). Findings suggestive of these diseases include rapid or early-onset hirsutism, menstrual irregularities, hypertension, severe hirsutism, virilization, or pelvic masses (strength of recommendation [SOR]: **B**, based on a cohort study in a referral population) (**TABLE**). Hirsutism with unremarkable history and physical exam findings should be evaluated with a serum total testosterone and dehydroepiandrosterone sulfate (DHEAS) level (SOR: **B**, based on a cohort study in a referral population).

CLINICAL COMMENTARY

Early work on expectations by physician and patient leads to a better outcome

Primary care physicians field questions about nonspecific findings on a day-to-day basis. Hirsutism is a common complaint and physical finding in women. Most diagnoses related to hirsutism are not life-threatening and have a relatively straightforward workup. There is the occasional patient with a zebra-type diagnosis that demands more detailed evaluation. As with most physical findings that have a large subjective component, I find that early management of expectations both on the part of the physician and patient leads to a better outcome whether or not a million-dollar workup shows any definitive pathology.

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Evidence summary

Hirsutism is the presence of excess terminal hairs in androgen-dependent areas on a female, and can be measured objectively using a scoring system such as the modified Ferriman-Gallway (mF-G) score. This test is done by adding hair scores (0=none, 4=frankly virile) in 9 different body locations. A total score >8 is considered hirsute. The incidence of hirsutism in the US is about 8%, based on a prospective study of 369 consecutive women of reproductive age seeking pre-employment physicals in the southeastern US using the mF-G criteria.[1]

The causes of clinically apparent androgen excess, including acne and hirsutism, were evaluated in 1281 consecutive patients presenting to a university endocrinology clinic.[2] Researchers excluded 408 subjects due to the inability to assess hormone status or ovulatory function. The remaining 873 women were assessed by clinical exam, mF-G score, serum total and free testosterone, DHEAS, and 17-hydroxy-

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FAST TRACK

With an unremarkable history and exam, order serum total testosterone and dehydroepiandrosterone sulfate levels

progesterone (17-HP). Hyperandrogenism was defined as an androgen value above the 95th percentile of 98 healthy control women (total testosterone ≥88 ng/dL, free testosterone ≥0.75 ng/dL, or DHEAS ≥2750 ng/dL). Those with a 17-HP level >2 ng/mL had either a repeat 17-HP or adrenocorticotropic hormone (ACTH) stimulation test. Those with at least 2 total testosterone levels above 250 ng/dL or those with signs of an androgen-secreting neoplasm (eg, virilization) underwent a transvaginal sonogram and a CT scan of the adrenals. Patients with ovulatory dysfunction had a thyroid-stimulating hormone (TSH) and prolactin level drawn. If Cushing's syndrome was suspected clinically, the subjects underwent an overnight 1-mg dexamethasone suppression test (**TABLE**). Of 873 patients, 75.5% had hirsutism and 77.8% had hyperandrogenemia. An identifiable disorder of androgen excess was found in 7%; functional androgen excess (principally PCOS) was identified in the remainder.

The incidence of endocrine disorders among patients presenting with hirsutism or androgenic alopecia was evaluated during a prospective study of 350 consecutive patients referred to an endocrine clinic in the UK.[3] Testing included serum total testosterone, androstenedione, 17-HP, and DHEAS on 2 occasions. Patients also underwent high-resolution pelvic ultrasound. Further investigations were done only for those with abnormal hormone levels or clinical findings suggestive of a tumor. Of 350 women tested, 13 had a markedly elevated serum total testosterone level >5 nmol/L (150 ng/dL). A single total testosterone test identified 6 of 8 patients with an underlying endocrine disorder. The other 2 had either acromegaly or prolactinoma. The researchers concluded that clinical assessment and a single serum total testosterone level were sufficient to exclude enzyme deficiencies and virilizing tumors.

A retrospective study of 84 consecutive women presenting to an endocrinology clinic in the Netherlands was conducted to determine hormone level sensitivity and specificity to identify virilizing adrenal tumors.[4] Hormone levels of 14 women with either an adrenal carcinoma (n=12) or an adrenal adenoma (n=2) were compared with the hormone levels of the women with hirsutism (n=73) as well as to the controls (n=31). Serum levels of total testosterone, androstenedione, DHEAS, DHEA, and cortisol were measured. A 24-hour urinary 17-ketosteroid excretion was also measured. A 5-day dexamethasone suppression study was conducted and a urinary sample was obtained between 8 and 9 A.M. on Day 6. An elevated basal total testosterone (normal range, 29–84 ng/dL) or DHEAS level (normal range, 118–431 ng/dL) detected all 14 women with adrenal carcinomas or adenomas and 36 of 73 women with hirsutism of non-neoplastic origin. The combined test sensitivity was 100% (95% confidence interval [CI], 77–100) and specificity was 50% (95% CI, 38–62) for the detection of adrenal tumors.

A prospective study of the incidence of late-onset CAH among hirsute women evaluated 83 consecutive patients with hirsutism from an endocrinology clinic in California with an ACTH stimulation test.[5] They found 1 patient with late-onset CAH. Because CAH had an incidence of only 1.2% (95% CI, 0.0–3.4), the authors concluded that routine testing with the ACTH stimulation test is not cost-effective for the evaluation of hirsutism.

Recommendations from others

The American College of Obstetrics and Gynecology 1995 technical bulletin recommended using the clinical examination to guide the evaluation, and laboratory testing to rule out androgen-producing tumors including a serum total testosterone and DHEAS.[6] The Society of Obstetricians and Gynaecologists of Canada advised using the clinical examination to guide the assessment, and a total serum testosterone level and a DHEAS level.[7]

Referral is recommended in the presence of virilism or if the total testosterone or DHEAS level is over twice the upper limit of normal or if there are signs of Cushing's disease.

TABLE

Differential diagnosis of clinically apparent androgen excess

DIAGNOSIS	INCIDENCE	KEY HISTORY/EXAM FINDINGS	ADDITIONAL TESTING
Polycystic ovarian syndrome	82.0%	± irregular menses, slow-onset hirsutism, obesity, infertility, diabetes, hypertension, family history of PCOS, diabetes	Fasting glucose, insulin and lipid profile, blood pressure, ultrasound positive for multiple ovarian cysts
Hyperandrogenism with hirsutism, normal ovulation	6.8%	Regular menses, acne, hirsutism without detectable endocrine cause	Elevated androgen levels and normal serum progesterone in luteal phase
Idiopathic hirsutism	4.7%	Regular menses, hirsutism, possible overactive 5 alpha-reductase activity in skin and hair follicle	Normal androgen levels, normal serum progesterone in luteal phase
Hyperandrogenic insulin-resistant acanthosis nigricans (HAIR-AN)	3.1%	Brown velvety patches of skin (acanthosis nigricans), obesity, hypertension, hyperlipidemia, strong family history of diabetes	Fasting glucose and lipid profile, BP, fasting insulin level >80 µIU/mL or insulin level >300 on 3-hour glucose tolerance test
21-hydroxylase non-classic adrenal hyperplasia (late-onset CAH)	1.6%	Severe hirsutism or virilization, strong family history of CAH, short stature, signs of defeminization, more common in Ashkenazi Jews and Eastern European decent	17-HP level before and after ACTH stimulation test >10 ng/dL, CYP21 genotyping.
21-hydroxylase-deficient congenital adrenal hyperplasia	0.7%	See *Late-onset CAH.* Congenital virilization	17-HP levels >30 ng/dL
Hypothyroidism	0.7%*	Fatigue, weight gain, history of thyroid ablation and untreated hypothyroidism, amenorrhea	TSH
Hyperprolactinemia	0.3%†	Amenorrhea, galactorrhea, infertility	Prolactin
Androgenic secreting neoplasm	0.2%	Pelvic masses, rapid-onset hirsutism or virilization, over age 30 with onset of symptoms	Pelvic ultrasound or abdomen/pelvic CT scan
Cushing's syndrome	0%‡	Hypertension, buffalo hump, purple striae, truncal obesity	Elevated blood pressure, positive dexamethasone suppression test

*Five patients were previously diagnosed with hypothyroidism and 1 patient was diagnosed as part of the work-up for a total prevalence of 6 in 873 or 0.7% although the de novo incidence was only 0.1%.
†Two patients were previously diagnosed with hyperprolactinemia and 1 was detected during the work-up for a total prevalence of 3 in 873 or 0.3% although the de novo incidence was 0.1%.
‡No patients were identified with Cushing's syndrome in this study. Other published reports vary from 0-1% (3).
Source: Azziz et al, *J Clin Endocrinol Metab* 2004[2]; Azziz, *Obstet Gynecol* 2003.[8]

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